

ASSOCIATIONS AMONG PHYSICAL ACTIVITY, PERCEPTION OF STRESS, AND
RELAPSE OCCURRENCE IN MULTIPLE SCLEROSIS

BY

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THESIS

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ABSTRACT

Background: Relapsing-remitting multiple sclerosis (RRMS) is a chronic, immune-mediated disease that is characterized by relapses or periods of worsening symptoms (Lublin & Reingold, 1996). The occurrence of a relapse has been associated with experiencing a stressful event (Mohr, Hart, Julian, Cox, & Pelletier, 2004). Physical activity could potentially influence relapse occurrence directly or indirectly through attenuation of the stress response, but neither of these relationships have been investigated in people with MS. Two theoretical models, the Transactional Model of Stress and Coping and the Cross-Stressor Adaptation Hypothesis, could possibly provide an explanation for how stress is involved in the relationship between physical activity and relapse occurrence.

Objective: The two aims of this retrospective study were to determine: 1) Is physical activity associated with a decreased number of relapses within a year; and 2) Is the relationship between physical activity and relapse occurrence mediated or moderated by stress?

Methods: The sample included 47 females with RRMS who had characteristics for increased risk of relapse occurrence (female, short disease duration, young age of adult onset). Participants completed the Perceived Stress Scale (PSS), Modified Activity Questionnaire (MAQ), and a recall of any relapses during the previous year. Participants further wore a pedometer for 7 days.

Results: Nineteen or 40% of the participants had a relapse during the previous year. There were statistically significant differences between those who did and did not have a relapse in the previous year for pedometer steps ($t = 2.13, p < 0.05$), PSS ($t = -2.05, p < 0.05$), and MAQ ($t = 1.96, p < 0.05$). The occurrence of a relapse was positively associated with PSS ($r = .29$) and negatively associated with MAQ ($r = -.29$) and pedometer ($r = -.30$). The regression analyses for mediation effects showed the relationship between physical activity (i.e. both pedometer and MAQ separately) were slightly attenuated, but non-significant when relapse occurrence was regressed on both physical activity and PSS. For moderation, pedometer steps were significantly correlated with relapse in the low stress group ($r = -.435$) but not in the high stress group ($r = -.076$), and MAQ was significantly correlated with relapse occurrence in the high stress group ($r = -.345$), but not in the low-stress group ($r = -.207$).

Conclusion: Physical activity was moderately, significantly, and inversely related to relapse occurrence in persons in the early stages of RRMS. This means that physical activity behavior could potentially be a determinant of relapse occurrence or that inactivity could be a consequence of having a relapse. There were weak and inconsistent results with perception of stress as a mediator or moderator of the relationship between physical activity and relapse occurrence in MS. These results did not fully support the Transactional Model of Stress and Coping or the Cross-Stressor Adaptation Hypothesis for understanding the decrease in relapses seen with physical activity in persons with MS.

To my parents and grandparents

*Thank you for always encouraging me
to follow God, to dream big, to do my best
and “leave it all on the table”*

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CHAPTER 1

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease where the myelin sheath, axons and nerve cell bodies in the central nervous system (CNS) are damaged (Vosoughi & Freedman, 2010). The etiology of disease is thought to be a T-cell mediated autoimmune disorder, where the immune defense system targets and attacks the myelin sheath and transects neuronal axons, forming lesions in the white matter (McFarland & Martin, 2007). Recently, widespread neuronal degeneration in the grey matter has been noted as a component of the MS pathogenesis, particularly in advanced disability (McFarland & Martin, 2007). Overall, the disease course does not follow a standard blueprint, but instead has, “unpredictable patterns of evolution and widely variable timetables,” that mainly depend on the characteristics of the individual (Vollmer, 2007, p. S7).

The majority of MS patients have a disease course marked by acute episodes of decreased neurological function (i.e. relapses) followed by partial or complete recovery. This disease course is called relapsing-remitting multiple sclerosis (RRMS), and affects about 85-90% of persons diagnosed with MS (Buljevac et al., 2003; Lublin & Reingold, 1996). By definition, a relapse is the worsening of existing symptoms or the development of new symptoms that persist for more than 24 hours and appear after at least 30 days of stability (Buljevac et al., 2003). Relapses are a clinical representation of increased inflammatory activity, demyelination, and neuronal damage within the brain, spinal cord, or optic nerves, which present in a variety of problematic symptoms including numbness, paralysis, and loss of vision (Compston & Coles, 2002; Compston & Coles, 2008). The relapse frequency (i.e. the relapse rate) is variable

depending on the characteristics of the person (i.e. gender, age) and of the disease (i.e. type, course, duration). According to a review on relapse rate in MS clinical trials, relapse rate tends to be higher in younger, female patients with shorter disease duration and lower disability (Held et al., 2005).

Experiencing a stressful life event has been associated with an increased risk of a relapse in individuals with RRMS (Mohr, Hart, Julian, Cox, & Pelletier, 2004). One meta-analysis explored this relationship between stress and relapses in MS and reported that higher incidences of stress were correlated with increased relapse rates (Mohr, Hart, Julian, Cox, & Pelletier, 2004). Fourteen studies were included in this meta-analysis and yielded a mean weighted effect size of $d = 0.53$ between stressful events and a relapse occurrence. This association between stress and a relapse is stronger than the overall effect of disease-modifying drug therapies on reducing exacerbations within the first year ($d = 0.36$; Mohr, Hart, Julian, Cox, & Pelletier, 2004; Filippini et al., 2003).

Physical activity is another factor than may be linked with relapse rate. Historically, physicians discouraged their patients from engaging in physical activity because of the long-held belief that exercise would lead to increases in core body temperature and promote disease activity (Uhthoff, 1889; Schulz et al., 2004). Physical activity has now been shown to have a positive impact on symptomology and fitness levels in MS (White & Dressendorfer, 2004), and relapse rate has not appeared to increase with exercise training or high levels of physical activity (Mostert & Kesselring, 2002). To date, this relationship between physical activity and relapse occurrence in the MS population has not been directly examined. Further research on this relationship would provide insight on whether physical activity behavior influences relapse occurrence in early RRMS, as a clinical marker of short-term disability. The primary hypothesis

for this study was that physical activity would be linked with a lower relapse rate because of its association with stress.

There are two possible mechanisms by which physical activity could influence the stress response and alter relapse rate, through psychological or physiological adaptations. The Transactional Model of Stress and Coping suggests that changing the perception of stress, control, or self-efficacy of the individual could impact the perception of how often or how long a stressor is considered threatening or insurmountable (Glanz & Schwartz, 2008). Higher levels of physical activity are associated with decreases in perceived stress and improvements in self-efficacy, which could result in fewer relapses and less disease activity in this population. For the Transactional Model, stress would act as a mediator of the relationship between physical activity and relapse occurrence in MS. Whereas, the Cross-Stressor Adaptation Hypothesis indicates that more physically active or fit individuals would have an attenuated response to stressful events, likely because of decreased CNS activation and immune suppression (Buckworth & Dishman, 2002). This adaptation hypothesis suggests that stress would moderate the relationship between physical activity and relapse occurrence, and that a differential relationship would be seen between high and low stress groups (Figure 1).

The primary purpose of this retrospective study was to examine the relationships among physical activity, perceived stress, and relapse occurrence in women recently diagnosed with RRMS. The specific aims of the study were to determine 1) if physical activity was associated with decreased number of relapses within a year; and 2) if the relationship between physical activity and relapse occurrence was mediated or moderated by stress (Figure 1).

CHAPTER 2

LITERATURE REVIEW

2.1 MULTIPLE SCLEROSIS: ETIOLOGY, PREVALENCE, AND CLINICAL COURSE

Multiple sclerosis (MS) is an chronic, immune-mediated disease, where the immune system mistakenly labels and attacks normal functioning cells in the CNS as foreign antigens (Smith, 2008). In MS, the myelin and oligodendrocytes, the cells that produce myelin, are attacked and sometimes the neuronal axons are irreversibly damaged (Smith, 2008). Since the myelin sheath acts as an insulator surrounding the neuron and allowing for saltatory conduction of action potentials, any damage to the myelin sheath inhibits and sometimes destroys neurological signaling (Smith, 2008). This demyelination and axonal injury in the CNS is predominant during the early stages of the disease and widespread neuronal degeneration of white and grey matter is seen more in the latter stages of the disease (Smith, 2008; Dutta & Trapp, 2007; McFarland & Martin, 2007).

MS is the most common chronic disabling disease of the CNS in young adults and affects about 2.5 million people worldwide and approximately 400,000 Americans, with an incidence rate of about 7 new cases per 100,000 each year (Confavreux, Vukusic, Moreau, & Adeleine, 2000; Compston & Coles, 2002). Most individuals are diagnosed with MS between the ages of 20 to 50 years, with twice as many cases for women than men and higher prevalence rates in northern countries (Mitsonis et al., 2008). Although neurological disability increases over time with the disease, life expectancy remains relatively the same; most individuals will live at least 25 years after diagnosis and cause of death is usually unrelated to the disease (Compston &

Coles, 2002). There are four classifications of MS subtypes that were outlined by Lublin and Reingold on behalf of the National Multiple Sclerosis Society (1996):

- Relapsing-remitting (RRMS) – a disease course marked with distinct episodes of worsening neurologic functioning followed by periods of partial or complete remission
- Secondary-progressive (SPMS) – a disease course starting in a relapsing-remitting pattern that transitions into a secondary phase of continuous neurologic decline
- Primary-progressive (PPMS) – a disease course distinguished by a slow worsening of neurologic function from onset, with no distinct relapses or remissions
- Progressive-relapsing (PRMS) – a disease course characterized as a gradual worsening of symptoms from onset, punctuated by superimposed relapses

Relapsing-remitting MS (RRMS) is the most common type of disease course, affecting about 85% of persons diagnosed with MS (Compston & Coles, 2002; Lublin & Reingold, 1996). The majority of MS cases start with a relapsing-remitting disease course and eventually enter into a progressive phase where little to no recovery occurs, with an estimated 90% of persons converting from RRMS to SPMS by ≥ 25 years of disease duration (Vollmer, 2007; Confavreux & Vukusic, 2006). Generally as the disease progresses, a decline in inflammation and relapse rate is accompanied by a steady rise in axonal degeneration and brain volume loss (Figure 2; Vollmer, 2007).

2.2 RRMS: DEFINITION AND CLINICAL PREDICTORS OF RELAPSE RATE

Relapsing-remitting MS is characterized by periods of exacerbated symptoms (i.e. relapses) followed by full or partial recovery (i.e. remissions; Vollmer, 2007; Lublin & Reingold, 1996). A relapse in MS is the clinical representation of demyelination and disruption of neural conduction, which presents itself through heterogeneous symptomology (Compston & Coles,

2002). In general, a relapse is clinically diagnosed by the sudden appearance of new symptoms or worsening of old symptoms that do not coincide with a fever or infection (Ackerman et al., 2002). A relapse can be defined as “the occurrence, reoccurrence, or worsening of symptoms of neurologic dysfunction,” that last for more than 24 hours and eventually resolve partially or completely (Confavreux, Vukusic, Moreau, & Adeleine, 2000 p. 1431). In general, the relapse frequency for a person with RRMS is about 0.69 relapses a year ($N = 126$; Smolders, Menheere, Kessels, Damoiseaux, & Hupperts, 2008), but there are many individual predictors that can increase the relapse rate. Some of these clinical predictors of relapse rate are type and duration of disease and personal characteristics like gender and age.

Most research studies report the highest relapse rate among participants with relapsing-remitting type of MS and within their first five years after onset. The type of MS (i.e. RRMS or SPMS) is a predictor for relapse rate, with RRMS patients reporting a higher on-study relapse rate than SPMS patients; 303 RRMS patients (90% of RRMS sample) reported 2 or more relapses in the previous 24 months compared to 132 SPMS patients (33% of SPMS sample; Held et al., 2005). In a separate study, the mean relapse rate was 1.17 relapses a year for those diagnosed with RRMS and in the first five years after diagnosis (Smolders, Menheere, Kessels, Damoiseaux, & Hupperts, 2008). Early in the disease course (i.e. first 3.6 years), relapse rate averages about 1.1 relapses per year, which declines with advancing disease duration (Patzold & Pocklington, 1982). Typically annualized relapse rate steadily decreases after disease onset with an average 17% reduction every 5 years after diagnosis (Figure 3; Tremlett, Zhao, Joseph, Devonshire, & UBCMS Clinic Neurologists, 2008).

Gender and age can also be important factors that influence relapse rate. Natural history cohorts have shown higher annual relapse rates in younger patients as well as in females

compared to male participants (Held et al., 2005). According to large cross-sectional study, the highest annualized relapse rate compared to all other age groups was in females in their second decade of life (Figure 3; Tremlett et al., 2008). Within the first two years after diagnosis, females in their twenties and thirties (i.e. *M* age at disease onset = 32 years) have the highest relapse rate, with an average of 1 relapse a year (Binquet et al., 2006). Overall, relapse rate tends to be higher in younger, female patients with RRMS, short disease duration, and lower disability (Held et al., 2005). Collectively, a sample with these features should yield an ideal sampling window for studying relapse occurrence.

2.3 PATHOPHYSIOLOGY OF A RELAPSE IN MULTIPLE SCLEROSIS

Relapses are considered to be a reflection of an acute or subacute focal inflammation in the CNS that results in damaged myelinated neurons and disruption of neurological signaling (Vollmer, 2007). Relapses in RRMS have been associated with demyelination, axonal transection, and remyelination (Compston & Coles, 2002), which means that relapse occurrence is “related to the temporally and spatially segregated effects of activated autoreactive T cells,” (Vollmer, 2007, S7). The pathophysiology of a relapse involves autoreactive T cells crossing the blood-brain barrier, releasing interferon gamma and other cytokines, and activating endothelial and glial cells that draw mononuclear cells from blood vessels into the CNS (Vollmer, 2007). This proinflammatory response involving cytokines and autoreactive antibodies infiltrating the CNS leads to demyelination and irreparable, axonal damage in the white matter.

2.4 CONSEQUENCES OF A RELAPSE

The consequences of a relapse include disease factors like disease progression and worsening of disability as well as patient factors like psychological functioning, social involvement, and financial costs of treatment (Coyle & Johnson, 2007). The occurrence of a

relapse has been associated with subsequent impairment and disability in patients with RRMS (Lublin, Baier, & Cutter, 2003; Hirst et al., 2008). In a placebo-controlled study, 95 patients had a residual deficit of at least 0.5 in the Expanded Disease Status Scale (EDSS) score units from before to after an exacerbation, and 63 of those patients had a deficit of at least 1.0 or more units (Lublin, Baier, & Cutter, 2003). In another large study with 182 patients, the mean residual change in EDSS score from pre to post relapse was 0.5 points and partial or complete recovery was not influenced by gender, age, or site of lesion (Hirst et al, 2008). These findings suggest that relapses impact long-term disability in persons with MS.

The occurrence of a relapse can also have negative impact on the emotional, psychological, and social health of the patient. Since the symptoms experienced during a relapse usually involve physical or cognitive changes, the occurrence of relapse is “always considered a ‘crisis’ that disrupts the status quo for both patient and family” (Kalb, 2007, p. S29). There is a wide array of feelings that are commonly expressed by people with MS and their loved ones, including grief, anxiety, anger, and guilt, in relation to their loss of function or control with a relapse (Kalb, 2007). The physical or cognitive changes that occur during a relapse can strain coping mechanisms and have a profound effect on the social involvement, employment, and the roles of partnership and in the family that fulfill a patient (Halper, 2007).

Furthermore, physical inactivity could possibly be a consequence of relapse occurrence for patients in early RRMS. This relationship has not been directly measured yet, but the worsening of symptoms over a 3-5 year period in persons with MS has shown to decrease the level of self-reported physical activity significantly and moderately (Motl, Arnett, Smith, et al., 2008). The sudden worsening of symptoms seen with a relapse could potentially have the same impact, and lead to an immediate decrease in physical activity following a relapse.

2.5 STRESS AND ITS RELATIONSHIP WITH RELAPSES IN RRMS

Ever since the first documented case of MS, the role of stress has been thought to be involved in disease progression and relapse occurrence (Charcot, 1877; Mohr, Hart, Julian, Cox, & Pelletier, 2004). A stressor is “any severe challenge or threat to the normal process or integrated function of a living thing,” and the stress response can be considered the compensatory reaction of the body to restore homeostasis after experiencing this external disturbance (Lovallo, 2005, p. 38). The inability of the body to cope properly and restore homeostasis after exposure to a stressor can lead to biological or psychological damage and possibly death (Mohr, 2007).

The general physiologic stress response of the body was first theorized by Hans Selye (1956) and his primary findings with animals exposed to a stressor were 1) a reduction in the size of immune system organs including the thymus gland, 2) growth of the adrenal gland, and 3) the appearance of ulcers in the gastrointestinal tract (Selye, 1956; Lovallo, 2005). This nonspecific response pattern was coined the general adaptation syndrome (GAS) with three distinct stages: 1) alarm reaction, 2) stage of resistance, 3) stage of exhaustion (Selye, 1946). Prospectively, the occurrence of relapse would happen during the stage of resistance because there is evidence that persons with RRMS have on average 14.0 ± 3.0 days between stressor and relapse occurrence (Ackerman et al., 2002). The stage of resistance can involve the release of glucocorticosteroids, the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, and alteration in mediators like autonomic CNS neurotransmitters and inflammatory cytokines (McEwen & Wingfield, 2003). The idea that stressful events like grief, vexation, and physical trauma trigger an inflammatory response that influences disease factors such as relapse occurrence in persons with MS has been speculated (Mohr, 2007).

Several recent studies including meta-analytic, longitudinal, and prospective studies have reported evidence of a consistent relationship between stress and relapse occurrence in MS. A meta-analysis including 14 empirical studies found a significant association between stressful life events (SLEs) and relapse incidence with an average weighted effect size of $d = 0.53$ (Mohr, Hart, Julian, Cox, & Pelletier, 2004). This effect size was moderate in magnitude (Cohen, 1988), indicating the significant impact of stress on relapse occurrence in persons with RRMS. A longitudinal study with 23 RRMS and SPMS female patients reported an average annual relapse rate of 2.6 relapses per year and 85% of those relapses were associated with one or more SLEs occurring in the 6 weeks prior (Ackerman et al., 2002). In a prospective study, 55 persons diagnosed with RRMS showed a 3.7 greater likelihood of having an exacerbation after exposure to stressful events compared to those not exposed (Franklin, Nelso, Heaton, Burkes, & Thompson, 1988). These findings support the existence of a relationship between stress and the occurrence of a relapse in persons with MS.

The link between stress and relapse occurrence has been suggested to be attributed to glucocorticoid (GC) resistance in persons with MS, because MS patients have been speculated to have compromised immune cells that are less sensitive to the regulatory effects of GC (Mohr & Pelletier, 2006; DeRijk, Eskandar, & Sternberg, 2004). When a specimen is exposed to a stressor, they show a pro-inflammatory response with elevated levels of IL-6 cytokine released into the plasma, and those with GC resistance are not able to regulate or stop this immune response (Huang, Takaki, & Arimura, 1997; Takaki, Huang, Somogyvari-Vigh, & Arimura, 1994; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993; Meagher et al., 2007). Overall, the relationship between stress and relapse occurrence has been well documented in persons with MS and could be possibly driven by immune dysfunction.

2.6 PHYSICAL ACTIVITY AND RELAPSES IN MULTIPLE SCLEROSIS

The impact of physical activity on disease activity and disability progression in MS is a growing topic of research, but the direct relationship between physical activity and relapses has remained unexplored. For over a century, clinicians have discouraged their patients from engaging in physical activity because of the belief that high levels of activity would worsen symptoms and increase relapse frequency based on thermosensitivity in MS (Uhthoff, 1889; Schulz et al., 2004). Starting in 1984, this myth about physical activity has been dispelled with research studies showing that exercise has a positive impact on fitness levels, depression, fatigue, and quality of life in persons with MS (Gehlsen, Grigsby, & Winant, 1984; Mostert & Kesselring, 2002).

Recently, many exercise interventions have been administered to samples of MS patients and researchers have confirmed that exercise is safe for patients with MS (Romberg et al., 2004). In multiple studies, minimal to no drop outs were reported because of relapse occurrence or disease progression during an exercise intervention (Romberg et al., 2004; Mostert & Kesselring, 2002; Schulz et al., 2004). In a 4-week exercise training program, only 6% of participants reported temporary symptom impairment, but these increased symptoms were not reported as a clinical relapse (Mostert & Kesselring, 2002).

Physical activity has been determined to be a behavioral correlate to short-term disability progression in persons with MS, specifically in those with RRMS and minimal disability (Motl & McAuley, 2011). At the end of the 6-month study, those who experienced a relapse during the study had an increase in disability status at follow-up (path coefficient = 0.07, $p = 0.01$) and follow-up disability status was associated with physical activity (path coefficient = -.09, $p = 0.025$; Motl & McAuley, 2011). By extension, these findings provide some support for a

relationship between physical activity and relapse occurrence because short-term disability was associated with both physical activity and relapse occurrence in this sample (Motl & McAuley, 2011).

Over the past 30 years, the belief that physical activity leads to relapse occurrence has been discarded, but still no research studies have directly examined the existence or direction of a relationship between physical activity and relapses in MS.

2.7 RELATIONSHIP BETWEEN PHYSICAL ACTIVITY, STRESS, AND RELAPSES

Historically, physical activity has been deemed a buffer for stress in healthy, nondiseased persons and has been suggested as a moderating factor between stress and the development of physical symptoms (Carmack, Boudreaux, Amaral-Melendez, Brantley, & de Moor, 1999). In a study with 135 college students, students dealing with high stress who engaged in low levels of leisure physical activity experienced around 37% more physical symptoms and 21% more anxiety compared to those engaging in high levels of physical activity (Carmack, Boudreaux, Amaral-Melendez, Brantley, & de Moor, 1999). Aerobic training in a sample of highly stressed police officers has also shown physical and psychological improvements, including gains in cardiovascular fitness, reductions in perceived job stress, and enhancements in quality of life (Norris, Carroll & Cochrane, 1990). These findings suggest that individuals who engage in higher levels of physical activity are less susceptible to the consequences of stress, such as anxiety and physical symptoms.

Multiple theoretical constructs have been devised to determine the mechanism in which physical activity decreases the stress response. The Transactional Model of Stress and Coping attributes changes in stress response to psychological adaptations (i.e. perception of control, self-efficacy), whereas the Cross-Stressor Adaptation Hypothesis attributes decreases in the stress

response to physiological adaptations (i.e. cardiovascular reactivity, HPA response). Although these theories are unproven and have not yet been applied to the MS population, physical activity could be an agent for altering stress response and decreasing relapse occurrence in persons with MS.

2.7.1 Psychological Adaptation: Transactional Model of Stress and Coping

Physical activity has been postulated to counteract the consequences of a stressful event, by changing the perception of stress and self-efficacy of the individual to cope with the stressor. The Transactional Model of Stress and Coping defines stressful events as transactions between an individual and their environment and stress is considered to be the imbalance or deficit between environmental demands and personal resources (Lazarus & Folkman, 1984; Lazarus & Cohen, 1977; Cohen, 1984). The model proposes that when an individual is exposed to a stressor they undergo two types of appraisal: primary appraisal, where the individual evaluates the significance of an event and its associated threat or harm; and secondary appraisal, where the individual evaluates the controllability of the stressor and their coping resources to alter the situation or manage their emotional reaction (Glanz & Schwartz, 2008). According to the model, altering the primary or secondary appraisal of the stressor would improve the adaptability of the individual to the stressor.

Physical activity has been shown to decrease perception of stress (i.e. primary appraisal) and increase self-efficacy (i.e. secondary appraisal) in general adult and specific disease populations. In a study with healthy older adults, participants were assigned to an exercise group where they walked at a pace of 60% of maximum heart rate (HR), for 1 day per week for 10 weeks (Starkweather, 2007). The participants in the exercise group reported a significant reduction in perceived stress using the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein,

1983) and significant improvements in physical functioning, vitality, and mental health (Starkweather, 2007). In a study with HIV patients, a six-month supervised aerobic and resistance program showed a significant increase in self-efficacy, specifically in how they deal with stress from the disease and other life events (Fillipas, Oldmeadow, Bailery, & Cherry, 2006). These findings support the notion that engaging in regular physical activity could lead to psychological adaptations, such as decreases in the perception of stress and increases in coping ability that could influence the stress response and possibly decrease disease activity in persons with MS.

2.7.2 Physiological Adaptations – Cross-Stressor Adaptation Hypothesis

Since the 1990s, researchers have claimed that attenuations in the stress response seen with exercise training are due to physiological adaptations. Evidence has shown that repeated bouts of exercise (i.e. high levels of physical activity) lead to cardiovascular and autonomic adaptations such as reductions in resting HR and BP levels and increased vagal dominance (Hagberg, Park, & Brown, 2000; Tulppo et al., 2003). A meta-analysis examining 30 methodologically rigorous studies showed that more fit individuals expressed lower cardiovascular reactivity (i.e. HR and systolic BP reactivity) to an acute psychological stressor, compared to more unfit individuals (Forcier et al., 2006). In a study with older adults, a 10-week exercise intervention showed a significant decline in IL-6 levels, which is pro-inflammatory cytokine that increases after exposure to a stressor (Starkweather, 2007). All of these physiological adaptations are benefits of engaging in regular physical activity which seem to be universal across healthy and diseased populations.

The Cross-Stressor Adaptation Hypothesis was developed because of the similarities between exercise and psychosocial stressors in their activation of central and peripheral

physiological systems (Sothmann et al, 1996). The theory predicts that a bout of exercise elicits a stress response that results in beneficial adaptations in bodily systems involved in the stress pathway, that transfer to psychosocial stressors (Hull, Young, & Ziegler, 1984; Salmon, 2001; Sothmann et al., 1996). Essentially, the Cross-Stressor Adaptation Hypothesis suggests that exercise training improves stress reactivity by altering cellular tissue structure, reducing neuroendocrine hormone release, and raising neural threshold (Sothmann, 2006). Physiological adaptations with exercise include decreasing cardiovascular reactivity, lowering circulating cytokines (i.e. IL-6), reducing HPA-axis response, and increasing biosynthesis and storage of catecholamines (i.e. norepinephrine and epinephrine; Sothmann, 2006). This hypothesis provides a logical argument for how regular physical activity could lead to an attenuated stress response and provide a useful strategy for reducing relapses and symptoms in persons with MS.

2.7.3 Theoretical summary and conclusions

In summary, these two theories provide plausible mechanisms for how physical activity could alter the stress response and decrease disease activity in persons with MS. Engaging in physical activity could potentially buffer the consequences of stress, by acting through one or both mechanisms, altering the psychological perceptions and/or the physiological systemic reactivity. The two mechanisms and their potential impact on stress and relapse occurrence are illustrated in Figure 4; the highlighted portions in the figure were the variables measured in this study.

2.8 SUMMARY AND CURRENT STUDY

Relapsing-remitting MS is a chronic, immune-mediated disease that is characterized by relapses or periods of worsening symptoms (Lublin & Reingold, 1996). Relapses are considered the clinical representation of demyelination and disruption of neural conduction in the CNS,

which results in new or old symptomology (Compston & Coles, 2002; Vollmer, 2007). Besides exacerbated symptoms, relapses in MS could lead to the progression of disability and majorly impact the emotional, psychological, and social well-being of the patient (Coyle & Johnson, 2007). The occurrence of a relapse has been associated with experiencing a stressful event in both meta-analytic reviews, longitudinal, and prospective studies (Mohr, Hart, Julian, Cox, & Pelletier, 2004; Ackerman et al., 2002). Importantly, physical activity could influence relapse occurrence directly or indirectly through attenuation in the stress response, but both of these relationships need further investigation. Two theoretical models, the Transactional Model of Stress and Coping and the Cross-Stressor Adaptation Hypothesis, provide potential mechanisms for how stress drives the relationship between physical activity and relapse occurrence.

This thesis investigated the relationship between physical activity and relapse occurrence and the role of stress in this relationship among a specific cohort of women with RRMS. The following hypotheses were addressed in this study: 1) Is physical activity associated with a decreased number of relapses within a year; and 2) Is the relationship between physical activity and relapse occurrence mediated or moderated by stress?

CHAPTER 3

METHODOLOGY

3.1 TARGET SAMPLE

This research was approved by a University Institutional Review Board, and all participants provided written informed consent. The sample was recruited from a pool of research participants residing in the United States, who either responded to a research advertisement posted on the National Multiple Sclerosis Society website or who previously participated in research studies within the Exercise Neuroscience Laboratory. Upon telephone contact, persons received a full description of the study and procedures and then underwent a brief screening for inclusion. The inclusion criteria for the sample were a definite diagnosis of relapsing-remitting MS (RRMS), female, age between 18 and 40 years, short disease duration (i.e. within the first 5 years of onset), and ambulatory without aide (i.e. cane, walker, or wheelchair). The inclusion criterion characteristics were selected to acquire a sample with a high annual relapse rate.

There were 55 females with RRMS who were interested in participating in the study and underwent screening. Of those persons, 52 satisfied the inclusion criteria and were enrolled in the study; each of these individuals was sent an informed consent document (ICD; Appendix A), a Yamax SW-200 pedometer, and a questionnaire packet through the U.S. postal service. Five individuals either declined further participation (n=1) or did not return the ICD and questionnaire packet (n=4) despite three follow-up attempts to contact them by phone, e-mail, or postal service. The final convenience sample was 47 participants with RRMS.

3.2 MEASURES

Age, gender, occupation, race, economic status, and disease history were collected using a standard self-report demographics questionnaire. Disease status was reported using the Patient Determined Disease Steps (PDDS) scale (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007), a self-report measure developed as a surrogate for the Expanded Disability Status Scale (EDSS; Kurtzke, 1983).

Physical activity history. To assess physical activity history, participants completed the Modifiable Activity Questionnaire (MAQ). The MAQ is a self-report assessment of different types of leisure and occupational physical activities completed during the 12 months prior, with specific questions concerning the mode, frequency, and duration of activities (Pereira et al., 1997; Vuillemin et al., 2005). In this study, the shortened, self-administered MAQ questionnaire was used; this version is widely accepted and frequently administered measure of physical activity history in adults (Vuillemin et al., 2000; Vuillemin et al., 2005; Kriska et al., 2006; Khawaji, Astermark, Askesson, & Berntorp, 2010). The MAQ has been shown to be a valid and reliable assessment of physical activity in adults, when compared to activity monitors and doubly labeled water testing (Kriska et al., 1990; Schulz, Harper, Smith, Kriska, & Ravussin, 1994). The participants were asked to circle any activities performed more than 10 times in the previous 12 months and then provide an estimate of how many months, times per month, and minutes per time. For data analysis, the average number of hours per week spent in physical activity was calculated for the previous 12 months (Kriska et al., 1990).

Current physical activity. To objectively measure current physical activity, participants were instructed to wear a pedometer (Yamax SW-200; Yamax Corporation, Tokyo, Japan) around their waist during waking hours and to record their pedometer step counts in a log each day for a

7-day period. Each pedometer was checked for accuracy using a brief walk test (500 steps at 3 mi/hr on a treadmill), and if the error exceeded 2% (i.e., 10 steps), then the pedometer was not used in the study. This particular brand of pedometer, a Yamax SW-200, has been considered to be an accurate, reliable, and valid monitor of physical activity in persons with MS. The Yamax SW-200 pedometer has exhibited accuracy with actual steps on three different treadmill walking speeds [67, 80, and 94 m/min] in persons with MS (Motl, McAuley, Snook, & Scott, 2005). The reliability of pedometers has been examined in a large sample of persons with MS ($N = 193$) and resulted in high intra-class correlation estimates of 0.93 for 7-days of monitoring and 0.80 for 3-days of monitoring (Motl, Zhu, Park, et al., 2007). Pedometer steps have been strongly correlated with other measures of physical activity both self-report questionnaires (Godin Leisure Time Exercise Questionnaire, $r = .51$) and accelerometry (MTI accelerometer, $r = .82$) in persons with MS (Gosney, Scott, Snook, & Motl, 2007). These findings support the use of pedometers as an accurate and reliable measure of physical activity in the MS population.

Perceived stress. The perception of stress was measured using the self-report questionnaire, Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). This scale contains 14 items describing psychosocial feelings and thoughts experienced over the previous month. For example, two of the stress items are “In the last month, how often have you felt confident about your ability to handle your personal problems?” and “In the last month, how often have you found that you could not cope with all the things that you had to do?” The items are rated on a 5-point scale ranging from 1 (Never) to 5 (Very often) and summed into a single score ranging between 14 and 70, with higher scores reflecting greater levels of perceived stress. The PSS scale was found to have sufficient internal and test-retest reliability and PSS scores have been positively correlated with life events scales (i.e. both in impact and number of stressful life

events) and with depressive and physical symptomology scales (Cohen, Kamarck, & Mermelstein, 1983). The PSS questionnaire has been employed in previous research with the MS population, and has shown improvements in appraised stress, independent of anxiety and depression scores, after 8 weeks of therapy sessions (Johnson, Frederick, Kaufman, & Mountjoy, 1999). Therefore the PSS scale is considered to be a valid measure for the perception of stress, and a construct independent of anxiety and depression.

Relapse occurrence. Relapses that occurred during the previous 12 month period were reported through a self-report questionnaire and recall evaluation conducted over the phone (Verdier-Taillefer, Roulet, Cesaro, & Alperovitch, 1994; Ackerman et al., 2002). Each relapse had to meet the following criteria: 1) the development of new symptoms or worsening of old symptoms that lasted longer than 48 hours, 2) the absence of fever or infection of any kind, 3) partial or complete improvement during the subsequent months, with at least 30 days remission between relapses (Ackerman et al., 2002). Only the relapses that met the criteria were included in data analysis.

3.3 PROCEDURES

Each participant was contacted and screened over the phone and had to meet the following criteria to be included in the study: A definite diagnosis of RRMS; ambulatory without a cane or walker; female sex; within the ages of 18 to 40 years. Every participant that met the inclusion criteria was sent an ICD, approved by the University Institutional Review Board. Participants were required to sign and date the ICD to be enrolled in the study. Each participant that was enrolled was sent a Yamax SW-200 pedometer and a battery of questionnaires through the U.S. postal service. Participants were asked to wear their pedometer for a 7-day period during waking hours and record their steps each day on a provided log. After wearing the pedometer for

7 days, participants were instructed to complete and return the log and questionnaire packet in the pre-addressed, pre-stamped envelope provided. Upon receiving the questionnaire packet, participants underwent a recall evaluation over the phone to ascertain the occurrence of any relapses during the previous 12 month period. Participants received \$15 remuneration and the pedometer for their involvement in the study.

3.4 DATA ANALYSIS

Descriptive and inferential analyses were performed in SPSS Statistics, Version 19.0 (IBM, Chicago, IL). Values are presented as mean score \pm standard deviation of mean score (SD) in the text and tables. Independent samples *t*-tests were conducted for examining differences in pedometer steps, MAQ, and PSS values between subsamples of those who did and did not experience a relapse during the previous year. The statistical significance of the *t*-value was based on a *p*-value of ≤ 0.05 for a one-tailed test. The magnitude of group differences between groups was expressed as Cohen's *d* (Cohen, 1988) using the difference in mean scores divided by the pooled standard deviation. Values for Cohen's *d* of .2, .5, and .8 were interpreted as small, moderate, and large, respectively (Cohen, 1988).

As hypothesized, perceived stress was examined as a mediator and moderator in the relationship between physical activity and relapse occurrence. By definition, a mediator accounts for the relationship between the independent variable (i.e. physical activity) and the outcome dependent variable (i.e. relapse occurrence; Baron & Kenny, 1986). The model of mediation from Baron & Kenny (1986) is illustrated in Figure 5A and assumes that there are two causal paths feeding into the outcome variable, a direct influence from the independent variable (*Path c*) and a direct influence from the mediator (*Path b*). To establish mediation, the following conditions must be met: (1) the independent variable must be significantly associated with the

outcome variable; (2) the independent variable must be significantly associated with the mediator; (3) the mediator must be significantly associated with the outcome variable; and (4) the impact of the independent variable on the outcome variable must be significantly less after controlling for the variance attributable to the mediator (Baron & Kenny, 1986; MacKinnon, Fairchild, & Fritz, 2007). The mediating effect of perceived stress on the relationship between physical activity and relapse occurrence was determined using multiple regression analyses: (1) relapse was regressed on physical activity in the first equation; (2) relapse was then regressed on both perceived stress and physical activity in the second equation. Separate regression analyses were performed for current and historical physical activity as independent variables.

For moderation effects, correlation analyses were performed using both parametric Pearson-product (r) and non-parametric Spearman rho rank-order (ρ) correlation coefficients (Mason, Tu, & Cauce, 1996). A moderator is defined as a qualitative or quantitative variable that affects the direction and strength of the relationship between the independent variable (i.e. physical activity) and the dependent outcome variable (i.e. relapse occurrence; Baron & Kenny, 1986). The model of moderation is diagrammed in Figure 5B, with three causal paths, the predictor (i.e. physical activity; *Path a*), the moderator (i.e. stress; *Path b*), and the product of the predictor and moderator (*Path c*) feeding into the outcome variable of relapse occurrence (Baron & Kenny, 1986). Moderation is supported if the relationship between relapse occurrence and physical activity differs depending on levels of the moderator, perceived stress. To establish different levels of the moderator, “high” and “low” stress groups were created using a median split of scores for the PSS scale (Mason, Tu, & Cauce, 1996). Then, correlation coefficients were calculated between activity (i.e. current and historical physical activity, separately) and relapse occurrence for each group.

CHAPTER 4

RESULTS

4.1 SAMPLE CHARACTERISTICS

The sample consisted of 47 females with a definite diagnosis of RRMS who had characteristics for increased risk of relapse occurrence (i.e., female, young age of adult onset, short disease duration). Age, disease duration, and disability status (i.e. PDDS) are provided in Table 1 for the overall sample ($N = 47$) and the two subsamples; those who experienced a relapse in the previous year ($n = 19$) or those who did not ($n = 27$) and one participant reported “unsure” for experiencing a relapse during the previous year and could not be placed in either group for inferential statistics. The median PDDS score for the overall sample was 0 (range = 0 – 5) and corresponded to normal ability (i.e., mild symptoms, mostly sensory due to MS, but no limitations to daily activities). The overall sample was mostly Caucasian (87%), married (70%), employed (87%), and educated (30% had some college education and 62% were college graduates) with a median annual household income of greater than \$40,000 (77%). There were no significant differences in demographic or clinical variables between the two subsamples.

4.2 DESCRIPTIVE AND INFERENTIAL STATISTICS

The descriptive statistics for perceived stress (i.e. PSS), current physical activity (i.e. pedometer steps), and physical activity history (i.e. MAQ average hours) are provided in Table 2. There were statistically significant differences between the groups in current physical activity ($t = 2.13, p < 0.05$), perceived stress ($t = -2.05, p < 0.05$), and physical activity history ($t = 1.96, p$

< 0.05). The Cohen's d between groups was moderate in magnitude for all the measures: current physical activity ($d = 0.64$), physical activity history ($d = 0.60$), and perceived stress ($d = 0.62$).

4.3 CORRELATION ANALYSIS

The bivariate correlations are in Table 3 with parametric and non-parametric correlations below and above the diagonal, respectively. Current physical activity (i.e. pedometer steps) and physical activity history (i.e. MAQ average hours) were strongly correlated ($r = .567, \rho = .462$) in the sample. Perceived stress (i.e. PSS) was significantly and moderately correlated with both current and historical physical activity ($r = -.315, \rho = -.357$; $r = -.283, \rho = -.315$, respectively). The occurrence of a relapse was similarly and significantly correlated with current physical activity ($r = -.300, \rho = -.329$), physical activity history ($r = -.287, \rho = -.282$), and perceived stress ($r = .284, \rho = .278$).

4.4 MEDIATOR EFFECTS

The previous correlation analysis showed that there were significant associations between physical activity (i.e. both current and historical), perceived stress, and relapse occurrence, which satisfied the requirements for mediation analysis. The regression analysis showed a significant relationship when relapse occurrence was regressed on current physical activity, but this relationship became non-significant when relapse occurrence was regressed on both physical activity and perceived stress. Importantly, a comparison between the first and second regression equations for current physical activity and relapse occurrence indicated a small decrease in beta coefficients from $-.306$ ($p = 0.027$) to $-.236$ ($p = 0.122$), respectively (Figure 6A). This indicates that perceived stress weakly, if at all, acted as a mediator in the relationship between current physical activity and relapse occurrence. Likewise, all the conditions for the test of mediation were satisfied for physical activity history and perceived stress was found to weakly mediate the

relationship between physical activity history and relapse occurrence. There was a small decrease in beta coefficients from $-.287$ ($p = 0.056$) to $-.225$ ($p = 0.143$), when controlling for perceived stress in the relationship between physical activity history and relapse occurrence (Figure 6B).

4.5 MODERATOR EFFECTS

The sample was initially divided using median split of PSS scores into groups of low stress (PSS score ≤ 38 , $N = 24$) and high stress (PSS score > 38 , $N = 22$). The descriptive statistics and correlations of physical activity and relapse occurrence are provided in Table 4 for each group. Current physical activity was significantly correlated with relapse occurrence in the low stress group ($r = -.435$, $p = -.509$), but not in the high stress group ($r = -.076$, $p = -.093$). This indicates that perceived stress does moderate the relationship between current physical activity and relapse occurrence, but in the opposite direction of the hypothesis. Physical activity history was significantly correlated with relapse occurrence in the high stress group ($r = -.345$, $p = -.437$), but not in the low-stress group ($r = -.207$, $p = -.158$). This indicates that perceived stress does moderate the relationship between physical activity history and relapse occurrence, consistent with the direction proposed in the hypothesis.

CHAPTER 5

DISCUSSION

The main results of the study were that: 1) physical activity was significantly associated with relapse occurrence in women with RRMS, 2) perceived stress acts weakly, if at all, as a mediator between physical activity and relapse occurrence, and 3) though there is conflicting evidence, perceived stress acts as a moderator of the relationship between physical activity and relapse occurrence.

The primary finding of this study was that current and historical physical activity (i.e. pedometer steps and MAQ hours) were both moderately and significantly associated with relapse occurrence in women with early RRMS. This relationship between physical activity and relapse occurrence indicates that persons with MS who maintain a high level of physical activity report fewer relapses. This relationship has never been studied before directly, but previous research has suggested the possibility that physical activity would have a positive impact on relapse occurrence, similar to the relationship between physical activity and short-term disability in MS (Motl & McAuley, 2011). This novel finding has clinical significance because persons in the early stages of RRMS could potentially use physical activity as an inexpensive, noninvasive method for decreasing disease activity.

The secondary finding of the study was that physical activity was correlated with perceived stress in persons with MS, indicating that those who more physically active report less perceived stress. Previous research in nondiseased, adult populations has shown similar results with high levels of physical activity being associated with decreases in perceived stress, anxiety, and low quality of life (Norris, Carroll, & Cochrane, 1990; Carmack, Boudreaux, Amaral-

Melendex, Brantley, & de Moor, 1999). Physical activity has been suggested as an important health-promoting behavior for decreasing other psychosocial conditions like depression in persons with MS, specifically those who are in the early stages of the disease (Suh, Motl, & Mohr, 2010). Therefore, physical activity behavior could lead to reductions in perceived stress in the early stages of disease, when persons are more vulnerable to experiencing a relapse.

In this study, the role of perceived stress as a mediator or moderator of the relationship between physical activity and relapse occurrence was analyzed, in order to extend previous research on stress and relapse rate in MS. The rationale for these analyses was based on the well documented relationship between experiencing a stressful life event and relapse occurrence in persons with MS (Mohr, 2007; Mohr, Hart, Julian, Cox, & Pelletier, 2004). Perceived stress weakly, if at all, mediated the relationship between physical activity and relapse occurrence, in both current and historical physical activity. This finding indicates that perceived stress does not mediate and account for the relationship between physical activity and relapse occurrence, and that these two variables are related regardless of perceived stress. Perhaps physical activity works through a biological mechanism like the immune system to influence relapse occurrence in persons with MS. Exercise training has shown a significant decline in pro-inflammatory cytokine IL-6 levels in older adults (Starkweather, 2007). By lowering plasma levels of IL-6, exercise could provide a protective effect against relapses in persons with MS.

As for moderation, the results were mixed and conflicting, with perceived stress acting as a moderator for both current and historical physical activity, but in opposite directions. Physical activity history moderately correlated with relapse occurrence in the high stress group, and not as much with the low stress group, which was consistent with our hypothesized model (Figure 1). This finding indicates that physical activity behavior over the previous 12 months seemingly

buffers the influence of stress on relapse occurrence in persons with MS. Persons who were more physical active over the previous 12 months reported fewer relapses, in both the high and low stress group, but those in the high stress showed a much steeper decline in relapses with physical activity. However, the opposite finding was discovered with current physical activity; current physical activity had a significant relationship with relapse occurrence in the low stress group, but not in the high stress group. The high stress group maintained relatively low levels of physical activity, no matter if they experienced a relapse or not, this may mean that stress acted as a barrier for them engaging in physical activity. The finding with the low stress group could actually capture more of the reciprocal nature of the variables measured; this finding could be interpreted that those who have low stress and experience a relapse during the previous year become less physical active compared to those who do not experience a relapse. This moderation analysis suggests that there could possibly be reciprocal relationships between, 1) relapses and stress, and 2) relapses and physical activity.

Implications for theory can be made based on the correlational, mediation, and moderation analyses. The Transactional Model of Stress and Coping proposes that adaptations to the perception of stress, control, or self-efficacy of the individual could have a major impact on coping, and in turn disease activity in persons with MS. Evidence shows that patients with RRMS who believe they elicit some control over their health and the course of events in their life, experience fewer clinical relapses (Lasar & Kotterba, 1993; Mitsonis, Potagas, Zervas, & Sfagos, 2009). Full mediation of perceived stress would have provided support for the Transactional Model of Stress and Coping, but the results showed a weak, nearly non-existent, mediation between physical activity and reported relapses. The Cross-Stressor Adaptation Hypothesis proposes that physiological adaptations received from exercise training improve the

efficiency of the stress response and can transfer over to any novel, psychological stressors (Sothmann et al., 2006). The moderation analysis provided partial support for the Cross-Stressor Adaptation Hypothesis, because there was conflicting evidence found between current and historical physical activity. These inconsistent results for the moderation analysis prevent us from providing complete support for the Cross-Stressor Adaptation Hypothesis in persons with MS. Neither of these two mechanisms completely explains the involvement of perceived stress in the relationship between relapse occurrence and physical activity in persons with MS.

The major strengths of the study are the inclusion of a defined sample with the likelihood of a high annualized relapse rate and the use of two different measures of physical activity, current and historical physical activity. Another strength and novel feature of the study was the measure of perceived stress, instead of individual stressful life events. Nevertheless, there are several limitations to this study including the retrospective study design and inconsistency in the duration of assessment time periods among perceived stress, physical activity, and relapse occurrence. The retrospective design of the study precludes inferences about direction for causality among variables. Another limitation was that current physical activity and perceived stress were measured over one week and a month, respectively, whereas relapse evaluation and historical physical activity were measured over the previous 12 months. Also, relapse occurrence was measured using a valid self-report questionnaire and recall evaluation, but this variable was not confirmed by a licensed neurologist. Lastly, we did not measure any physiological markers like heart rate, blood pressure, vagal tone, or immune cytokines, to determine physiological adaptations with physical activity.

Future directions of research include a longitudinal examination of the relationship between physical activity and relapse occurrence and further investigation into the physiological

and psychological adaptations seen with physical activity. There needs to be a longitudinal examination of the relationship between physical activity, perceived stress, and relapse occurrences, in order to examine the levels of activity and perceived stress before, during, and after a relapse. Physical inactivity and stress could potentially be antecedents and consequences of relapses in persons with RRMS. As for physiological adaptations, researchers should investigate whether an exercise intervention leads to physiological advances in cardiovascular fitness and immune function that affect the stress response and decrease the number of relapses in person with RRMS. For the psychological adaptations, future research could look at whether perception of control, coping resources, and self-efficacy act as mediators between physical activity and relapse occurrence in persons with RRMS.

In conclusion, maintaining regular, moderate to high levels of physical activity may be beneficial for persons with MS, in managing their stress and in reducing their annual relapse rate. Females with early RRMS who maintain a more active lifestyle report having less perceived stress and fewer relapses throughout a year. There were weak and inconsistent results with stress as a mediator or moderator of the relationship between physical activity and relapse occurrence in MS. These results did not fully support the Transactional Model of Stress and Coping or the Cross-Stressor Adaptation Hypothesis as theoretical constructs for understanding the decrease in relapses seen with physical activity in persons with MS. The novel finding of this study is that physical activity was moderately and significantly related to relapse occurrence in persons in the early stages of RRMS, which means that physical activity behavior could potentially be a determinant of relapse occurrence or that inactivity could be a consequence of having a relapse.

Table 1

*Difference in demographic and clinical variables in the overall sample and between subsamples
(i.e. relapse, no relapse)*

	Overall (N = 47)	Relapse (N = 19)	No Relapse (N = 27)
Age (yrs)	34.7 ± 5.8	35.1 ± 5.5	34.3 ± 6.1
Disease duration (yrs)	2.7 ± 1.2	2.3 ± 1.1	2.9 ± 1.3
PDDS	0.8 ± 1.3	1.26 ± 1.3	0.5 ± 1.2

Note. Values are mean ± standard deviation. PDDS = Patient Determined Disease Steps.

Table 2

Descriptive and inferential statistics for current physical activity, physical activity history, and perceived stress for the overall sample and subsamples (i.e. relapse, no relapse)

	Overall (N = 47)	Relapse (N = 19)	No Relapse (N = 27)	<i>p</i> -value (one-tailed)	Cohen's <i>d</i>
Pedometer (steps/week)	5814 ± 3002	4705 ± 2467	6571 ± 3197	0.020	0.64
MAQ (average hrs/week)	3.54 ± 3.20	2.48 ± 2.45	4.34 ± 3.55	0.028	0.60
PSS	38.5 ± 8.6	41.6 ± 7.7	36.5 ± 8.8	0.023	0.62

Note. Values are mean ± standard deviation. PSS = Perceived Stress Scale; MAQ = Modifiable Activity Questionnaire.

Table 3

Correlations among Variables in the Sample of Relapsing-Remitting Multiple Sclerosis

Variable	1	2	3	4
1. Relapse occurrence	—	-.329*	-.282*	.278*
2. Pedometer (steps/week)	-.300*	—	.462**	-.357**
3. MAQ (average hrs/week)	-.287*	.567**	—	-.315*
4. PSS	.284*	-.315*	-.283*	—

Note. *Correlation is significant ($p < .05$), **Correlation is significant ($p < .01$). Values below diagonal are parametric correlations (r) and values above diagonal are non-parametric correlations (ρ). PSS = Perceived Stress Scale; MAQ = Modifiable Activity Questionnaire.

Table 4

Moderation effects of perceived stress on the relationship between physical activity and relapse occurrence

Groups	Overall	Relapse	No Relapse	Correlation
Current PA				
Low stress ($n = 24$)	6788 \pm 3053	4817 \pm 2307	7568 \pm 3014	$r = -.435^*$ $\rho = -.509^*$
High stress ($n = 22$)	4820 \pm 2673	4623 \pm 2686	5018 \pm 2776	$r = -.076$ $\rho = -.093$
Historical PA				
Low stress ($n = 24$)	5.36 \pm 3.55	3.91 \pm 2.50	5.27 \pm 3.96	$r = -.207$ $\rho = -.158$
High stress ($n = 22$)	2.14 \pm 2.08	1.44 \pm 1.91	2.84 \pm 2.08	$r = -.345$ $\rho = -.437$

Note. *Correlation is significant ($p < .05$). PA = physical activity. Parametric correlations (r) and non-parametric correlations (ρ). Low stress group has a PSS score ≤ 38 ; High stress group has a PSS score >38 .

Figure 1

Hypothesized model of the relationships between physical activity and relapse occurrence in persons with RRMS. The model includes both mediating and moderating relationships between physical activity and relapse occurrence

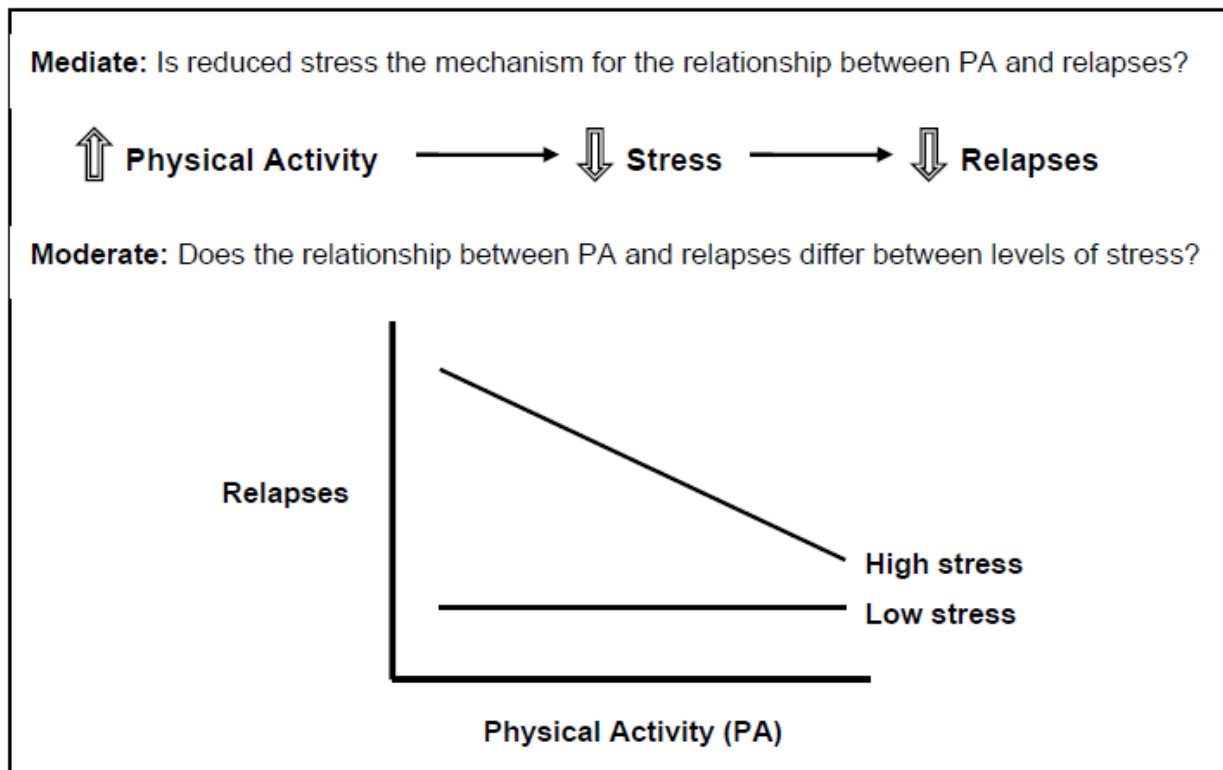


Figure 2

Inflammation and axonal loss in regards to disease progression in MS (Vollmer, 2007)

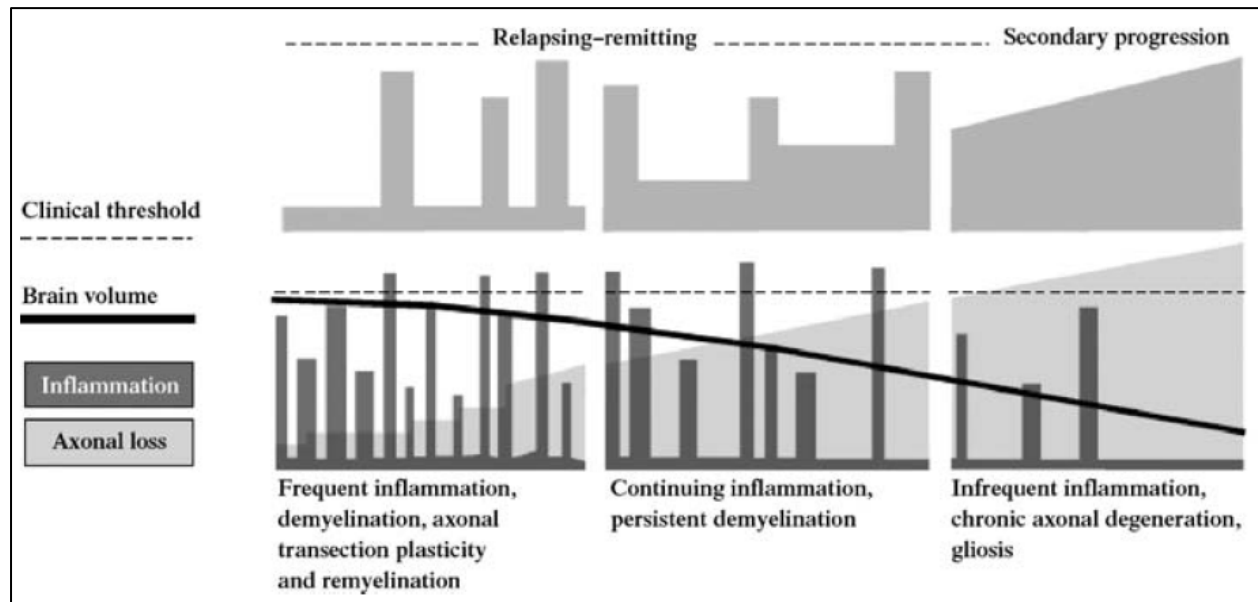
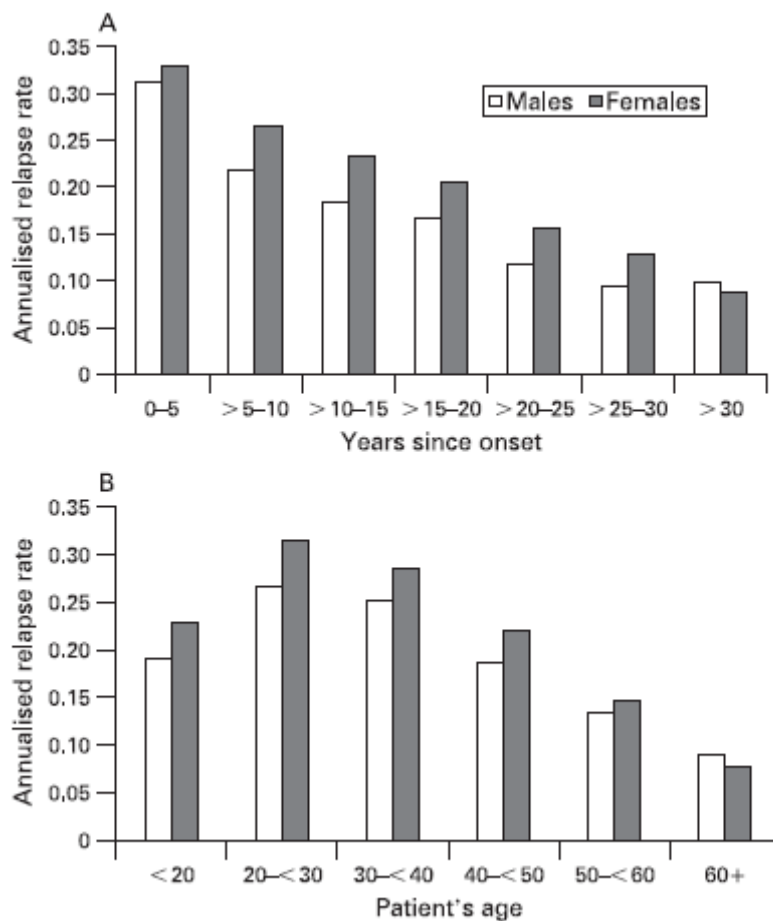


Figure 3

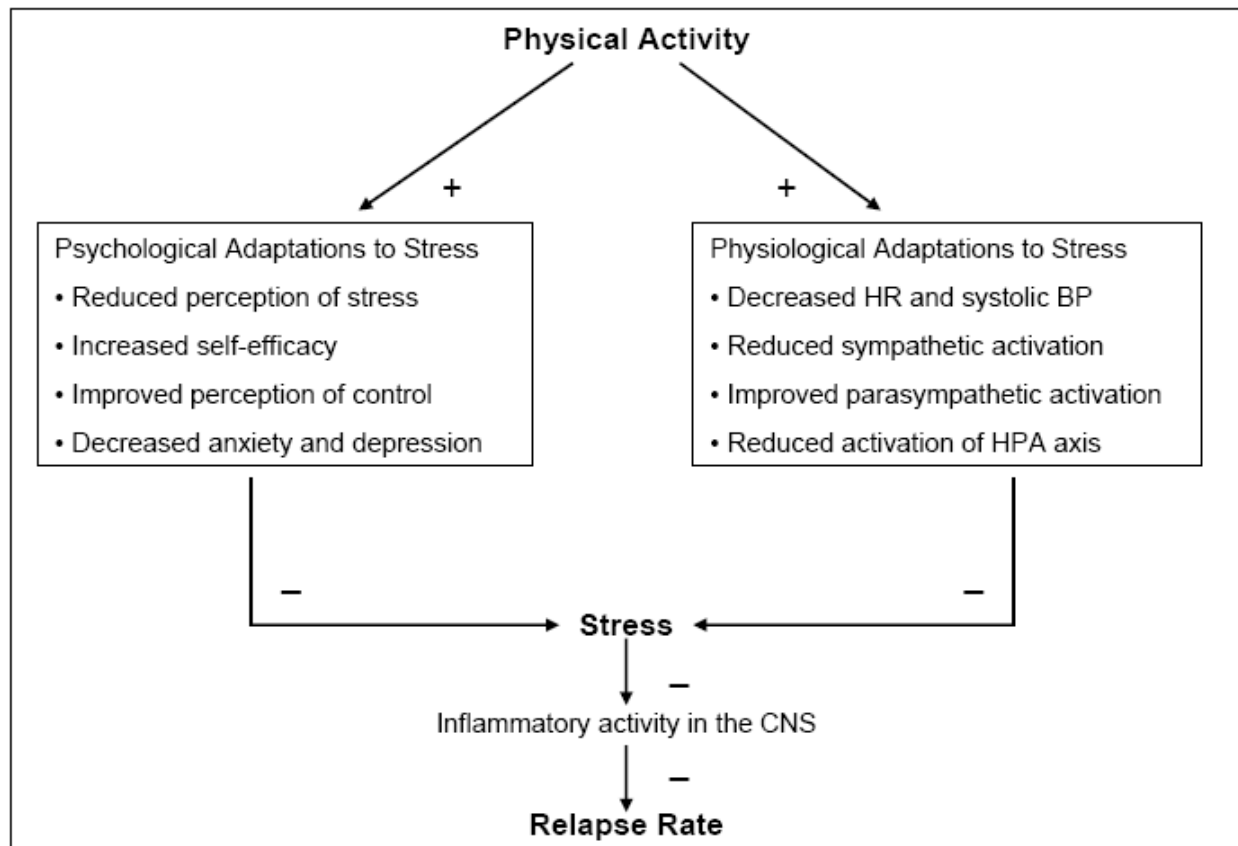
Relapse rate for men and women with RRMS or SPMS. Figure A is relapse rate for each year after disease onset (n = 2477) and Figure B is relapse rate in regards to patient's current age (n = 2477; Tremlett, Zhao, Joseph, Devonshire, & the UBCMS Clinic Neurologists, 2008).



Note. All relapsing at onset patents are considered (RR and SPMS). The onset relapse was excluded. Annualised relapse rate = (relapse count/number days contributed by each patient) x 365.25

Figure 4

Summary model for the interaction between physical activity and relapse rate in MS

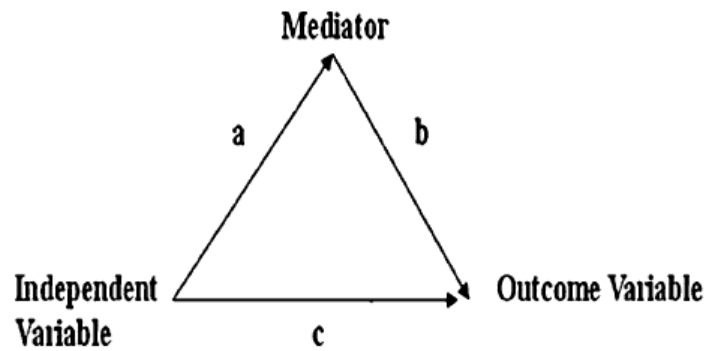


Note. The bolded variables were variables measured in the study and the (+, -) signs show the positive or negative relationships between the variables. HR = heart rate; BP = blood pressure; HPA = Hypothalamic-pituitary-adrenal.

Figure 5

Models of mediation and moderation from Baron & Kenny (1986).

A.



B.

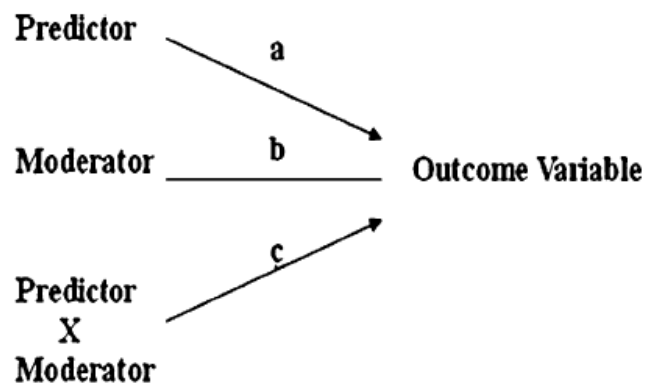
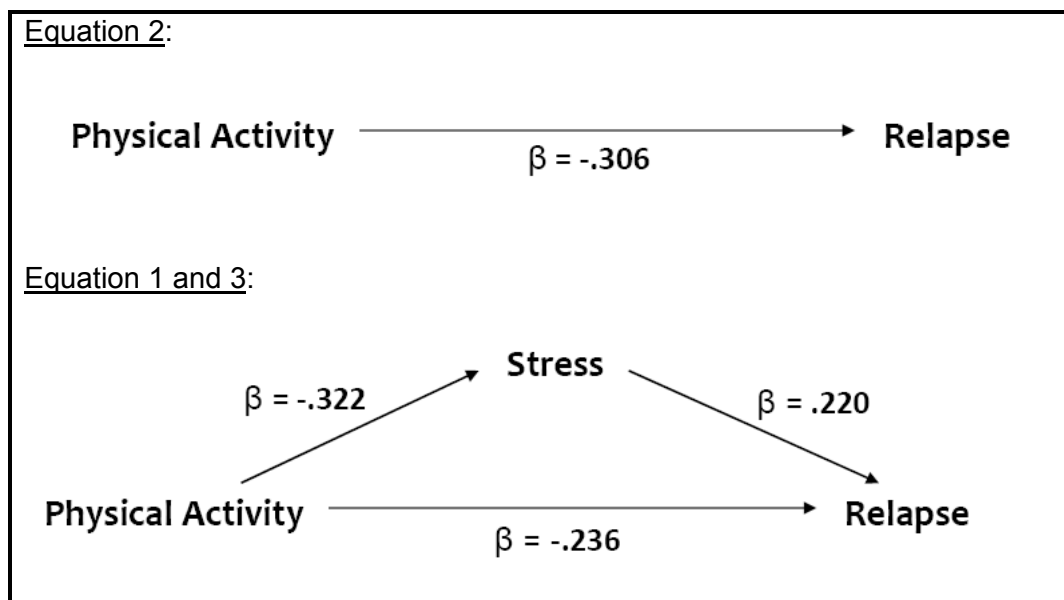


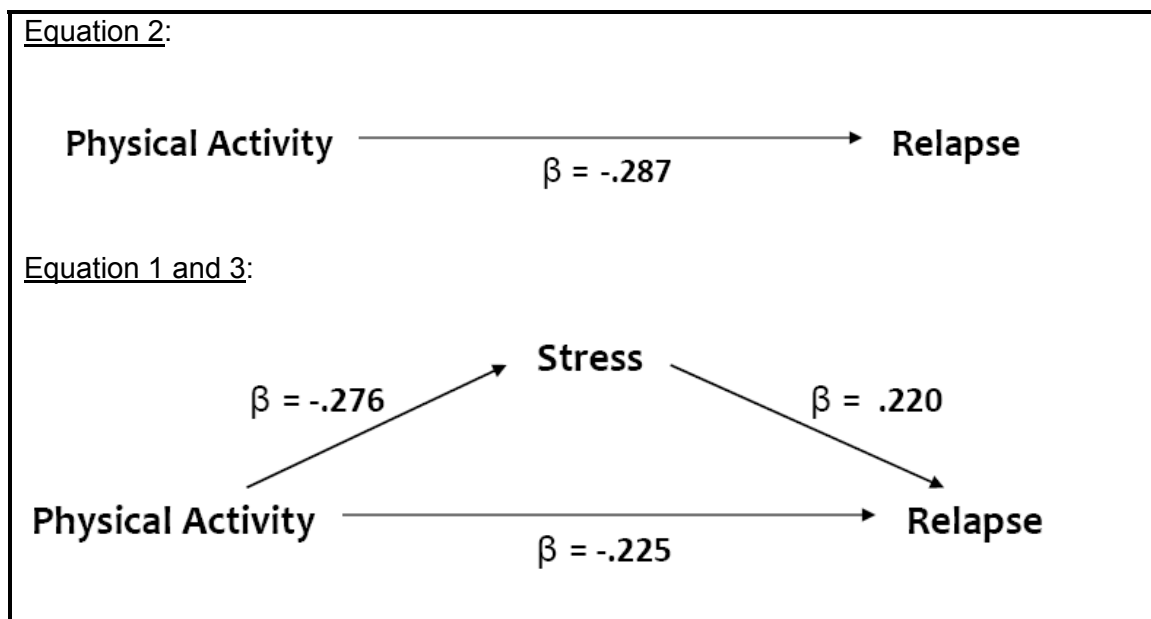
Figure 6

Mediating effects of stress on the relationship between current and historical physical activity on relapse occurrence in the sample of women with RRMS.

A. Current physical activity



B. Physical activity history



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APPENDIX A
INFORMED CONSENT

This appendix material is in the supplemental file named “09222_Approval_01142009.”

This appendix is the official informed consent document that was approved by the Institution Review Board (IRB) at the University of Illinois, Urbana-Champaign. The informed consent document with dated and stamped approval is included along with a letter from Sue Keehn, Director of Institution Review Board dated January 13, 2009. The official IRB protocol, UIUC number was 09222.

APPENDIX B

PERCEIVED STRESS SCALE

The supplemental file for this appendix material is “4.Perceived Stress Scale (PSS) 14-item.”

The Perceived Stress Scale (PSS) was a questionnaire that participants completed in the study to measure their perceptions, feelings, and thoughts over the previous month. There were 14 questions and each question had five options: Never, Almost Never, Sometimes, Fairly Often, and Very Often. The questions were designated to measure how often a participant felt or thought a certain way. For example, the first question on the PSS was “In the last month, how often have you been upset because of something that happened unexpectedly?”

APPENDIX C

MODIFIABLE ACTIVITY QUESTIONNAIRE

The supplemental file for this appendix material is “7.Modifiable Activity Questionnaire.”

The Modifiable Activity Questionnaire (MAQ) was a questionnaire that participants completed in the study that measured their involvement in physical activities throughout the previous 12 months. The questionnaire has 40 different options of common physical activities and participants were asked to circle all activities that they completed 10 or more times during the previous year. After circling their activities, they reported which months they engaged in each activity and then estimated the average amount of time spent in each activity. These data were used to determine the average number of hours spent in physical activity per week for each participant.

APPENDIX D

RELAPSE OCCURRENCE INTERVIEW

The supplemental file for this appendix material is “Baseline Exacerbation Recall.”

The Relapse Occurrence interview was conducted over the phone with each participant and the questions were to determine whether or not the participant had experienced a relapse during the previous 12 months. Participants were given a criteria for defining a relapse and then asked if and how many relapse they experienced during the previous 12 months. The rest of the questions in the interview focused on their most recent relapse called the “prior exacerbation” and participants were asked about the start and end date, severity of symptoms, and occurrence of a fever or infection. Then the participants were given a list of 25 common symptoms in multiple sclerosis and asked to identify and rank any of these symptoms that increased with the onset of their most recent relapse.